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(54) **3-Benzazepines as alpha-2 antagonists.**

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Description

This invention relates to pharmaceutical compositions comprising certain N-substituted 2,3,4,5-tetrahydro-1H-3-benzazepines and to compositions and compounds for use in producing alpha2 antagonism.

The pharmaceutical compositions of this invention produce alpha2 antagonism, a pharmacological action which is associated with the reduction of intraocular pressure and a broad spectrum of cardiovascular activity. For example, the compounds of this invention may be used for treating congestive heart failure, angina pectoris, and thrombosis.

Advantageously, the compounds also produce a reduction in blood pressure and are therefore useful as antihypertensive agents.

Reduction of intraocular pressure is of significant importance in the treatment of glaucoma which is a disease of the eye characterized by increased intraocular pressure. Glaucoma is a leading cause of blindness in people over forty. In poorly controlled glaucoma, the intraocular pressure is persistently increased and there is a progressive retinal and optic nerve degeneration. If untreated, a red painful eye may occur accompanied by reduced vision and eventually blindness.

The three agents most commonly used in glaucoma therapy are pilocarpine, timolol or epinephrine. Pilocarpine causes miosis and spasm of the ciliary muscle which produces blurred vision and myopia. Epinephrine dilates the pupil and blurs the vision as well as induces hyperemia, macular edema and allergic reactions in the eye. Moreover, systemic absorption of epinephrine after ocular instillation has produced cardiac arrhythmias. Timolol has few notable ocular side effects but systemic actions of the drug are a problem. Bradycardia, syncope, exacerbation of borderline congestive heart failure and bronchospasm have all been reported after topical timolol administration.

A still further disadvantage associated with epinephrine is that it is unstable to both air and light and subject to chemical attack by many agents that are conventionally used in pharmaceutical preparations. Attempts made to overcome these disadvantages usually resulted in compositions that were irritating to the body tissues or formed biologically inactive derivatives thereof.

This invention can therefore also be used to produce ophthalmic compositions which lower intraocular pressure which lack direct effect on pupil size, have no effect on heart rate or blood pressure in normotensive animals, and minimal local or systemic adverse effects upon instillation into the eye.

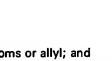
The novel compositions have been found unexpectedly to reduce intraocular pressure without the undesirable side effects and disadvantages of the prior art agents noted above.

Description of Prior Art

US—A—4,210,749 and US—A—4,233,217 disclose a broad class of benzazepines being useful as analgesics, antihistaminics and narcotic antagonists. GB—A—1268243 also discloses a broad group of compounds which comprise the compounds of Formula I. However, there is no specific disclosure of the compounds of Formula I. Moreover, there is no suggestion in these patents that the compounds of Formula I would be useful as alpha2 antagonists. Specific compounds of Formula I, 6-bromo- and 6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine have been disclosed as chemical intermediates in US—A—4,265,890. There is no suggestion in this patent that the compounds have any useful biological activity. US—A—3,716,639 and US—A—3,752,892 disclose 7-chloro and 6-chloro-2,3,4,5-tetrahydro-1H-3-benzazepines as anorexigenic agents. From these documents as well as from US—A—2520264 the therapeutical effects of the compounds of the invention could not be foreseen.

Description of Invention

The N-substituted 2,3,4,5-tetrahydro-1H-3-benzazepine compounds which are the active ingredients of the pharmaceutical compositions of this invention are represented by the following formula (I)



I

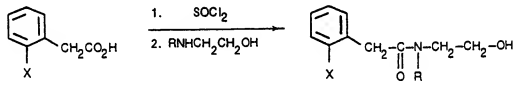
in which:

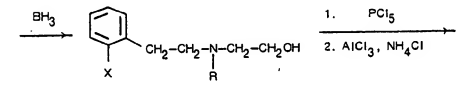
R is alkyl of from 1 to 3 carbon atoms or allyl; and

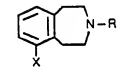
X is halogen such as chloro, bromo or fluoro, and a pharmaceutically acceptable acid addition salt thereof.

A particularly preferred compound in the pharmaceutical compositions of this invention is a compound of Formula (I) in which R is methyl and X is chloro being the compound 6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine.

The above compounds of Formula (I) which are the active ingredients in the compositions for producing alpha2 antagonism are prepared by synthetic methods familiar to the art. The most advantageous procedure is as follows:







The terms X and R are as defined above.

According to the above procedure, a halophenyl acetic acid is treated with thionyl chloride followed by an appropriate amino alcohol. The resultant amide is reduced by any well known agent such as, for example, borane. The resultant amino alcohol is then converted to the corresponding halide, such as chloride or bromide, and cyclized under Friedel-Crafts conditions. The cyclization step is carried out using Lewis acids, such as, for example, aluminum chloride, aluminum bromide, titanium chloride and antimony chloride. Advantageously the cyclization is carried out in a melt of aluminum chloride and ammonium chloride at elevated temperatures.

The compounds of formula (I) may also be prepared by reacting a 3-benzazepine compound in which R is hydrogen with an alkylating or acylating reagent which will replace the hydrogen with the desired R group. Such reagents include compounds of the formula RY and R^1COY wherein R is as defined above for formula (I), Y is halogen, such as chloro or bromo and R^1 is methyl or ethyl. Other reagents could include aldehydes or ketones.

When an aldehyde or ketone is used as the reagent it is followed by reductive alkylation. The reduction can be accomplished catalytically, such as with hydrogen and platinum, or chemically, such as with sodium borohydride or sodium cyanoborohydride.

When the reagent of the formula R^1COY is employed, the carbonyl moiety is subsequently reduced with, for example, lithium aluminum hydride.

The pharmaceutically acceptable acid addition salts having the utility of the free bases of formula (I), prepared by methods well known in the art, are formed with both inorganic or organic acids, for example: maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bis-methylenesalicyclic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicyclic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

The activity of the compounds of formula (I) is demonstrated *in vitro* by determining the prejunctional alpha2 antagonist activity using the isolated superfused guinea pig left atrium. Briefly, the heart is removed from a pentobarbital-anesthetized male guinea pig. The left atrium is removed, dissected free of extraneous tissue and mounted in a 2 ml. superfusion chamber. The tissue is paced at 60 pulse/minute and the sympathetic nerves excited at 6 minute intervals by field stimulation. The response to nerve stimulation is measured as the difference in contractile force between the basal contraction and peak contraction following a nerve stimulation. A concentration-response curve for clonidine (alpha2 agonist) is prepared by administering an increasing concentration of clonidine following each successive stimulation. The tissue is then superfused with the alpha2 antagonist to be tested for thirty minutes and the clonidine concentration-effect curve was repeated in the presence of antagonist. The receptor dissociation constant of the antagonist (KB) is defined as the antagonist concentration required to shift the log concentration-response curve of the agonist to the right by a factor of 2.

Selectivity for the alpha2 *vis-a-vis* the alphaladrenoceptor is determined by comparing the KB obtained as described above with the KB on the alphal receptor determined in the rabbit ear artery segment as an antagonist of the constrictor response induced by norepinephrine. (Hieble and Pendleton, *Arch. Pharmacol.*, 309, 217—224 (1979)).

A preferred compound of this invention is 6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine which has a KB value in the isolated perfused guinea pig left atrium of 13 nM.

When substitution is present at the 7-position of the benz-ring, a dramatic reduction in activity results. For example, the 7-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine has a KB value of 150 nM, i.e., about one tenth the alpha2 antagonist activity of the 6-chloro derivative. Further, when a substituent such as amino is present at the 6-position of the benz-ring, or the 6 and 7 positions are fused to a cyclopentane ring, the compounds are completely inactive as alpha2 antagonists.

The antihypertensive activity of the compounds of this invention is demonstrated *in vivo* as follows:

Male rats (300—450 g.) are anesthetized with sodium brevital and the femoral vein and artery are cannulated. Cannulas are run intradermally so as to be externalized in the dorso-sacral area of either side and kept in place by wound clips. The rats are allowed to regain consciousness after being placed in a small animal restrainer. The arterial cannula is connected to a pressure transducer for constant blood pressure and heart rate monitoring. Drugs are administered either orally via gavage or i.v. via the femoral vein cannula at a rate of 0.06 ml./minute.

The above test is conducted on both normotensive and hypertensive rats. DOCA Salt hypertensive rats are prepared from male uninephrectomized Sprague-Dawley rats. The rats, approximately six weeks of age, are lightly anesthetized with ether and subcutaneously implanted with a 25 mg. deoxycorticosterone acetate pellet in the left dorso-sacral area. Six days later a second pellet is implanted in the right dorso-sacral area. These rats are fed a normal laboratory diet, but are given 1% saline solution to drink in place of water. The rats are kept on the saline drinking water for 22—24 days.

The following table sets forth the effect of 6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine on blood pressure after i.v. administration to both normotensive and hypertensive rats.

TABLE 1

Type of Rats	Diastolic Blood Pressure		
	Pre Drug	Decrease BP (MMHg) 0.5 mg/kg	1.0 mg/kg I.V.
Normotensive (control) (Sprague-Dawley) (n = 4)	95 ± 7 MMHg	6 ± 2	13 ± 1
DOCA Salt Hypertensive (n = 4)	135 ± 5 MMHg	27 ± 3	33 ± 4
Normotensive (control) (Wistar-Kyoto) (n = 4)	115 ± 3 MMHg	7 ± 2	10 ± 2
Spontaneously Hypertensive (n = 7)	167 ± 3 MMHg	33 ± 7	46 ± 2

n = Number of rats

The data in Table 1 demonstrate that while 6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine has little effect on diastolic blood pressure in normotensive rats, it produced a marked drop in diastolic blood pressure in both DOCA Salt and spontaneously hypertensive rats. Moreover, comparison of the 0.5 mg/kg and 1.0 mg/kg doses shows that the antihypertensive effect is dose-related.

The effect of the oral administration of 6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine on blood pressure in the DOCA-salt hypertensive rat was also determined. Table 2 below sets forth the results of this test.

TABLE 2

Dose (PO)	Mean Arterial Pressure		Δ BP (MM Hg)
	Pre-Drug	Post-Drug	
2 mg/kg	148 ± 11	131 ± 12	17 ± 3
5 mg/kg	160 ± 7	127 ± 5	34 ± 4
10 mg/kg	167 ± 8	99 ± 4	68 ± 8

In addition, for cardiovascular use, the compositions of this invention may be combined with thiazide diuretics such as hydrochlorothiazide, triamterene, or calcium channel blockers such as Verapamil or Nifedipine, or β-adrenergic blockers such as propranolol. The amount of the substituted 3-benzazepines in the compositions of this invention would be in the ranges noted above combined with from 2 mg to 250 mg of the thiazide component. When combined with triamterene, from 5 mg to 250 mg of triamterene would be present. When a calcium channel blocker is employed in the compositions of this invention, from 1 mg to 500 mg would be employed.

A further activity of the compounds of this invention is demonstrated by their ability to reduce intraocular pressure. The measurement of intraocular pressure depends on subjecting the eye to a force that indents or flattens it. Either the effect of a particular force or the force for a given effect is measured. The specific procedure employed for the compounds of this invention is a normal rabbit intraocular pressure determination. A solution of 0.5% proparacaine hydrochloride diluted 1:10 with physiological saline is instilled into the eye of a rabbit. The lids are gently massaged over the cornea to insure good distribution of the solution. The eye is exposed by separating the lids and the tip of a probe is slowly placed on the cornea at the point where the curvature of the cornea is the greatest, i.e., on the optic axis. Employing an Alcon Applanation Pneumatonograph, the intraocular pressure is determined in each eye until a stable reading is obtained. West, C., Capella, J. and Kaufman, H., *Am. J. Ophthalmol.* 74:505 (1972).

Nine rabbits are used in each study, three animals for each dose in most circumstances. An initial, t=0, intraocular determination is made in both eyes. Immediately following the initial reading, the formulations to be tested, comprising concentrations of 0.01 to 10% of active ingredient, are instilled and pressure readings are taken at 0.5, 1, 2, 3, 4, and 6 hours post-instillation. The Intraocular pressure is determined from the value recorded on the pneumotonograph chart paper. A mean intraocular pressure value is calculated at each time point. A preferred compound of this invention, 6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine, decreases intraocular pressure at one hour by 3.5 mm of mercury relative to the untreated eye.

When the chloro was placed on the 7-position of the benzazepine nucleus and the compound was administered at the same doses, there was no lowering of intraocular pressure.

In summary, the structures of the compounds of this invention are specifically identified by having the halo at the 6-position of the benzazepine nucleus. As noted from the results of the test for alpha2 antagonism and the lowering of intraocular pressure, this is a critical feature of the compounds of this invention in order to obtain the desired biological activity. It was also unexpectedly discovered that when the preferred compound, 6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine, was given systemically and the above procedure was followed, intraocular pressure was lowered with no significant effect on systemic blood pressure. For example, when 0.5 mg/kg of the compound was infused in the ear vein in conscious normotensive rabbits, the compound decreased intraocular pressure at one hour by between 4 and 5 mm of mercury.

The pharmaceutical compositions used to carry out the method of producing alpha2 antagonism and antihypertensive activity comprise a pharmaceutical carrier and, as the active ingredient, a benzazepine compound of formula (I). The active ingredient will be present in the compositions in an effective amount to produce alpha2 antagonism and antihypertensive activity.

Preferably, the compositions contain the active ingredient of formula (I) in an amount of from 25 mg to 500 mg, advantageously from 50 mg to 250 mg, per dosage unit.

The pharmaceutical carrier may be for example a solid or a liquid. Exemplary of solid carriers are lactose, magnesium stearate, terra alba, sucrose, talc, stearic acid, gelatin, agar, pectin or acacia. The amount of solid carrier will vary widely but preferably will be from about 25 mg to 1 g. Exemplary of liquid carriers are syrup, peanut oil, olive oil, sesame oil, propylene glycol, polyethylene glycol (mol. wt. 200—400) and water. The carrier or diluent may include a time delay material well known to the art such as, for example, glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed, for example, the preparation may take the form tablets, capsules, powders, troches, lozenges, syrups, emulsions, sterile injectable liquids or liquid suspensions or solutions.

The pharmaceutical compositions are prepared by conventional techniques involving procedures such as mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

Preferably, the compounds of formula (I) are administered in conventional dosage unit forms prepared by combining an appropriate dose of the compound with standard pharmaceutical carriers.

Preferably, the active ingredient of formula (I) will be administered in a daily dosage regimen of from 100 mg to 1000 mg, most preferably from 200 mg to 500 mg. Advantageously, equal doses will be administered preferably two to four times per day.

The pharmaceutical compositions of this invention which reduce intraocular pressure comprise a pharmaceutical carrier, preferably an ophthalmic vehicle, and as the active ingredient an N-substituted 2,3,4,5-tetrahydro-1H-3-benzazepine of formula (I). The active ingredient will be present in the compositions of this invention in an effective amount to reduce intraocular pressure. Preferably, the compositions of this invention contain from 0.01% to 5.0% of the active ingredient of formula (I), advantageously, from 0.03% to 3.0%.

The ophthalmic vehicle or carrier may be, for example, a liquid or solid. Examplary of liquid ophthalmic carriers include standard 1.9% isotonic boric acid, 0.9% sodium chloride, or sodium borate solutions. Further, conventional phosphate buffer solutions such as the Sorenson phosphate buffer having a pH of 6.8 may be employed as the carrier. Exemplary of solid ophthalmic carriers may be typical ointment bases such as petrolatum.

The compositions of the present invention can be administered topically to the eye in dosage unit forms, such as, for example, ophthalmic solutions, ointments, creams, gels, or dispersions. When controlled release of the compound is desired, it may alternatively be incorporated into polymeric ocular insert systems which are well known to the art such as, for example, US—A—4,052,505.

The ophthalmic solutions are sterile and can contain in addition to the compound of formula (I) antimicrobrial agents. Exemplary of such agents are the quaternary ammonium germicides such as benzalkonium chloride, benzethonium chloride or cetylpyridium chloride. Other such agents that can be employed are chlorobutanol or phenylmercuric nitrate. If antioxidants are required, sodium sulfite, sodium ascorbate or other ophthalmologically acceptable antioxidants known to the art such as oxime sulfate may be used.

The benzazepine compound is preferably administered in ophthalmological dosage unit forms prepared by combining an appropriate dose of the compound with the above noted ophthalmological carriers. Preferably the ophthalmic dosage form is applied from two to four times daily. When an ophthalmic solution is employed one to drops may be administered two to four times a day.

When the administration is carried out as described above, alpha2 antagonism, antihypertensive activity and a lowering of intraocular pressure is produced.

The following Examples are illustrative of the compounds of this invention and processes for their preparation. The temperature are in degrees Centigrade.

A process for preparing compounds of formula (I) is claimed in our divisional application 84 116 509.5 (published as European Patent Application 0,161,350).

Example 1

A mixture of 125 g (0.73 mol) of O-chlorophenylacetic acid, 155 g (1.3 mol) of thionyl chloride and 2—3 drops of dimethylformamide in 1500 ml of toluene was stirred at room temperature for three hours. The toluene was evaporated under reduced pressure to give an oil which was dissolved in 200 ml of methylene chloride. This was added dropwise to a solution of 165 g (2.2 mol) of N-methylamino ethanol in 1 liter of methylene chloride. After addition was complete, the solution was stirred at room temperature for three hours. The organic solution was washed with water, dilute hydrochloric acid end saturated sodium chloride, dried over magnesium sulfate, filtered and evaporated to give 2-chloro-N-(2-hydroxyethyl)-N-methylbenzeneacetamide as a crystalline solid, m.p. 77°.

To 400 ml of a 1 mol solution of borane in tetrahydrofuran was added dropwise a solution of 43 g of the above amide in 350 ml of tetrahydrofuran at a rate sufficient to maintain a gentle reflux. After addition was complete, the solution was refluxed for two hours, cooled in an ice bath and treated carefully with dilute hydrochloric acid to destroy excess borane. The majority of the solvent was removed under vacuum and the residue heated on a steam bath for one hour. The mixture was diluted with 300 ml of water and extracted with ether. The aqueous layer was made basic with 40% sodium hydroxide and extracted with ether. The combined basic extracts were washed with water and saturated sodium chloride, dried and evaporated to give 2-[[2-(2-chlorophenyl)ethyl]methylamino]ethanol.

A suspension of 36 g (0.173 mol) of phosphorous pentachloride in 300 ml of methylene chloride was treated dropwise with a solution of 37 g (0.173 mol) of the 2-[[2-(2-chlorophenyl)ethyl]methylamino]ethanol in 150 ml of methylene chloride. After addition was complete, the mixture was refluxed overnight, evaporated to dryness and partitioned between dilute hydrochloric acid and ether. The aqueous layer was made basic with 10% sodium hydroxide and extracted well with ether. The ether extracts were washed with water and saturated sodium chloride, dried over magnesium sulfate and filtered. Addition of a saturated solution of ethereal hydrogen chloride gave a solid precipitate which was removed by filtration, washed with ether and dried to give 2-chloro-N-(2-chloroethyl)-N-methylbenzene ethanamine hydrochloride, m.p. 110°.

To a mixture of 41.5 g (0.155 mol) of the above chloro ethanamine hydrochloride and 6.26 g (0.117 mol) of ammonium chloride was added 41 g of anhydrous aluminum chloride. The reaction became homogenous, melted and exothermed. It was placed in an oil bath which had been heated to 175° and stirred for thirty minutes. An additional 20 g of aluminum chloride was added and the mixture heated for another thirty minutes. A final 41 g portion of aluminum chloride was added and the reaction heated for twenty hours. It was cooled to 140° and poured into 3 l of ice water containing 300 ml of concentrated hydrochloric acid and stirred for fifteen minutes. Sixty grams of sodium potassium tartrate was added and stirred until solution was effected. It was made basic with 40% sodium hydroxide, extracted twice with ether and the combined extracts washed with water, and saturated sodium chloride, dried and reduced in volume by half. Addition of a solution of saturated ethereal hydrogen chloride gave a solid precipitate which was collected, washed with ether and dried to give a white solid. Crystallization from methanol-ethyl acetate gave 6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, m.p. 268—270°.

Example 2

A stirred solution of 1.2 g of 6-chloro-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine in 30 ml of toluene was treated at 50° by dropwise addition with a solution of 0.7 g cyanogen bromide in 25 ml of toluene. Following the addition, the mixture was stirred and heated at 50° for one hour. A stream of nitrogen was passed over the surface of the solution during the reaction. The mixture was cooled, filtered and the filtrate concentrated in vacuo to yield 6-chloro-3-cyano-2,3,4,5-tetrahydro-1H-3-benzazepine melting at 81—82° from hexane-ether solution.

The 6-chloro-3-cyano-2,3,4,5-tetrahydro-1H-3-benzazepine was refluxed for 19 hours in a mixture of 30 ml of glacial acetic acid and 30 ml of 6N hydrochloric acid. The mixture was concentrated in vacuo to yield 6-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine as the hydrochloride salt of m.p. 214—215° from ethanol. This salt in turn gave the base 6-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine on treatment with dilute sodium hydroxide solution.

Example 3

A mixture of 0.52 g of 6-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine, 0.34 g of allyl bromide, 0.6 g of potassium carbonate and 20 ml of 90% ethanol was stirred at room temperature for 17 hours. The mixture was filtered and the filtrate concentrated in vacuo. The residue was extracted with 35 ml of ether and the ethereal extract treated with isoproponolic hydrogen chloride to precipitate 3-allyl-6-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride. Recrystallization of this salt from absolute ethanol gave 3-allyl-6-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride having a melting point of 248—249°.

Example 4

A solution of 1.5 g of 6-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine, 2.0 g of acetic anhydride and 20 ml of pyridine was stirred at room temperature for 3 hours. The mixture was concentrated in vacuo and the residue washed with 3N hydrochloric acid, then water, to yield 3-acetyl-6-chloro-2,3,4,5-tetrahydro-1H-3-benzazepine melting at 64—66°. This amide was reduced in ether with a 50% excess of lithium aluminum hydride at reflux for 6 hours. Upon decomposition of excess reducing agent, the reaction mixture was filtered and the ethereal filtrate dried over magnesium sulfate. The filtrate was treated with ethereal hydrogen chloride solution to precipitate 6-chloro-3-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine as the hydrochloride salt which melted at 274—275° from absolute alcohol.

Example 5

Following the procedure of Example 1 and substituting 2-[[2-(2-chlorophenyl)ethyl]ethylamino]-ethanol and 2-[[2-(2-chlorophenyl)ethyl]allylamino]-ethanol for 2-[[2-(2-chlorophenyl)ethyl]methylamino]-ethanol yields the following respective products: 6-chloro-3-ethyl-2,3,4,5-tetrahydro-1H-3-benzazepine and 6-chloro-3-allyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

Example 6

Ingredients		% W/W
6-Chloro-2,3,4,5-Tetrahydro-3-Methyl-1H-3-Benzazepine Hydrochloride		2.5 g
Benzalkonium Chloride		0.02 g
Sodium Bisulfite		0.10 g
Sterile Sodium Chloride Solution (0.9%) USP	qs	100 ml

The ingredients are dissolved in the sodium chloride solution. The solution is sterilized by filtration and aseptically packaged.

Two drops are instilled in the eye three times a day.

Example 7

Ingredients		% W/W
6-Chloro-2,3,4,5-Tetrahydro-3-Methyl-1H-3-Benzazepine		1.0 g
Purified White Petrolatum, U.S.P.	qs	100.0 g

Under aseptic conditions, the benzazepine is thoroughly incorporated in the petrolatum and packaged. The ointment is applied topically to the eye four times a day.

Example 8

Ingredients	Amounts
6-Chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine hydrochloride	150 mg
Lactose	350 mg

The ingredients are mixed and filled into a hard gelatin capsule. One capsule is administered four times a day.

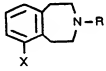
Example 9

Ingredients	Amounts
6-Chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine hydrochloride	200 mg
Calcium sulfate dihydrate	150 mg
Sucrose	25 mg
Starch	15 mg
Talc	5 mg
Stearic Acid	3 mg

The calcium sulfate dihydrate, sucrose and the benzazepine are thoroughly mixed and granulated with 10% gelatin solution. The wet granules are screened, dried and then mixed with the starch, talc and stearic acid, screened and compressed into a tablet.
One tablet is administered three times a day.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A pharmaceutical composition having alpha2 antagonist activity comprising a pharmaceutically acceptable carrier and a 3-benzazepine compound of the formula (I)



I

in which
R is alkyl having from 1 to 3 carbon atoms or allyl;
and
X is halogen;
or a pharmaceutically acceptable acid addition salt thereof.

2. A pharmaceutical composition as claimed in Claim 1 comprising 6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine.

3. A pharmaceutical composition as claimed in Claim 1 comprising 6-chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine hydrochloride.

4. A pharmaceutical composition for producing antihypertensive activity comprising a pharmaceutically acceptable carrier and a 3-benzazepine compound of formula (I) as defined in Claim 1.

5. A compound of formula (I) as defined in Claim 1 or a pharmaceutically acceptable salt thereof for use as an alpha2 antagonist.

6. 6-Chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine for use as an alpha2 antagonist.

7. 6-Chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine hydrochloride for use as an alpha2 antagonist.

8. A compound of formula (I) as defined in Claim 1 or a pharmaceutically acceptable salt thereof for use as an anti-hypertensive agent.

9. 6-Chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine for use as an anti-hypertensive agent.

10. 6-Chloro-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepine hydrochloride for use as an anti-hypertensive agent.

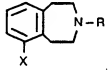
11. A process for preparing a pharmaceutical composition as claimed in Claim 1 which comprises mixing a compound of the formula (I) as defined in Claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

12. Use of a compound of formula (I) as defined in Claim 1 for the manufacture of a medicament for producing alpha2 antagonism.

13. Use of a compound of formula (I) as defined in Claim 1 for the manufacture of a medicament for the treatment of hypertension.

Claims for the Contracting State: AT

1. A process for preparing a pharmaceutical composition having alpha2 antagonist activity comprising a pharmaceutically acceptable carrier and a 3-benzazepine compound of the formula (I)



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in which

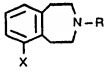
R is alkyl having from 1 to 3 carbon atoms or allyl; and

X is halogen;

or a pharmaceutically acceptable acid addition salt thereof which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Arzneimittel mit alpha2-Antagonisten-Wirksamkeit, umfassend einen pharmazeutisch verträglichen Träger und eine 3-Benzazepinverbindung der Formel I



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in der R einen Alkylrest mit 1 bis 3 Kohlenstoffatomen oder eine Allylgruppe bedeutet und X ein Halogenatom darstellt, oder ein pharmazeutisch verträgliches Säureadditionssalz davon.

2. Arzneimittel nach Anspruch 1, umfassend 6-Chlor-2,3,4-5-tetrahydro-3-methyl-1H-3-benzazepin.

3. Arzneimittel nach Anspruch 1, umfassend 6-Chlor-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepin-hydrochlorid.

4. Arzneimittel zur Erzeugung von Antihochdruckwirkung, umfassend einen pharmazeutisch verträglichen Träger und eine 3-Benzazepin-Verbindung der Formel (I) gemäß Anspruch 1.

5. Eine Verbindung der Formel (I) gemäß Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon zur Verwendung als alpha2-Antagonist.

6. 6-Chlor-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepin zur Verwendung als alpha2-Antagonist.

7. 6-Chlor-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepin-hydrochlorid zur Verwendung als alpha2-Antagonist.

8. Eine Verbindung der Formel (I) gemäß Anspruch 1 oder ein pharmazeutisch verträgliches Salz davon zur Verwendung als Antihochdruck-Wirkstoff.

9. 6-Chlor-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepin zur Verwendung als Antihochdruck-Wirkstoff.

10. 6-Chlor-2,3,4,5-tetrahydro-3-methyl-1H-3-benzazepin-hydrochlorid zur Verwendung als Antihochdruck-Wirkstoff.

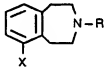
11. Verfahren zur Herstellung eines Arzneimittels gemäß Anspruch 1 durch Vermischen einer Verbindung der Formel (I) gemäß Anspruch 1 oder eines pharmazeutisch verträglichen Salzes davon mit einem pharmazeutisch verträglichen Träger.

12. Verwendung einer Verbindung der Formel (I) gemäß Anspruch 1 zur Herstellung eines Arzneimittels zur Erzeugung von alpha2-Antagonismus.

13. Verwendung einer Verbindung der Formel (I) gemäß Anspruch 1 zur Herstellung eines Arzneimittels zur Behandlung von Bluthochdruck.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines Arzneimittels mit alpha2-Antagonistenwirkung, das einen pharmazeutisch verträglichen Träger und eine 3-Benzazepin-Verbindung der Formel (I)



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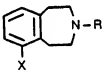
umfaßt, in der R einen Alkylrest mit 1 bis 3 Kohlenstoffatomen oder eine Allylgruppe bedeutet und X ein Halogenatom darstellt, oder einen eines pharmazeutisch verträglichen Säureadditionssalzes davon durch Vermischen einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon mit einem pharmazeutisch verträglichen Träger.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Une composition pharmaceutique ayant l'activité d'antagoniste d'alpha2, comprenant un support pharmaceutiquement acceptable et un composé de 3-benzazépine de la formule (I)



I

dans laquelle
R est alcoyle ayant entre 1 et 3 atomes de carbone ou bien allyle; et
X est halogène;
ou un sel d'addition d'acide pharmaceutiquement acceptable du même.

2. Une composition pharmaceutique comme indiqué à la revendication 1 comprenant 6-chloro-2,3,4,5-tétrahydro-3-méthyle-1H-3-benzazépine.

3. Une composition pharmaceutique comme indiqué dans la revendication 1 comprenant le chlorhydrate de 6-chloro-2,3,4,5-tétrahydro-3-méthyle-1H-3-benzazépine.

4. Une composition pharmaceutique pour la production de l'activité anti-hypertension comprenant un support pharmaceutiquement acceptable et un composé de 3-benzazépine de la formule (I), comme défini dans la revendication 1.

5. Un composé de la formule (I) comme défini dans la revendication 1 ou un sel du même pharmaceutiquement acceptable à employer en tant qu'antagoniste d'alpha2.

6. 6-chloro-2,3,4,5-tétrahydro-3-méthyle-1H-3-benzazépine à employer en tant qu'antagoniste d'alpha2.

7. Le chlorhydrate de 6-chloro-2,3,4,5-tétrahydro-3-méthyle-1H-3-benzazépine à employer en tant qu'antagoniste d'alpha2.

8. Un composé de la formule (I), comme défini dans la revendication 1 ou un sel du même pharmaceutiquement acceptable à employer en tant qu'agent antihypertension.

9. 6-chloro-2,3,4,5-tétrahydro-3-méthyle-1H-3-benzazépine à employer en tant qu'agent anti-hypertension.

10. Le chlorhydrate de 6-chloro-2,3,4,5-tétrahydro-3-méthyle-1H-3-benzazépine à employer en tant qu'agent anti-hypertension.

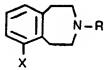
11. Un procédé pour la préparation d'une composition pharmaceutique comme indiqué dans la revendication 1 qui comprend le mélange d'un composé de la formule (I), comme défini dans la revendication 1 ou bien un sel du même pharmaceutiquement acceptable avec un support pharmaceutiquement acceptable.

12. L'emploi d'un composé de la formule (I), comme défini dans la revendication 1, dans la fabrication d'un médicament afin de produire l'antagonisme d'alpha2.

13. L'emploi d'un composé de la formule (I), comme défini dans la revendication 1, dans la fabrication d'un médicament pour le traitement de l'hypertension.

Revendication pour l'Etat contractant: AT

1. Un procédé pour la préparation d'une composition pharmaceutique ayant l'activité d'antagoniste d'alpha2 comprenant un support pharmaceutiquement acceptable et un composé 3-benzazépine de la formule (I)



I

dans laquelle
R est alcoyle ayant entre 1 et 3 atomes de carbones ou allyle; et
X est halogène;
ou bien un sel d'addition d'acide du même pharmaceutiquement acceptable qui comprend le mélange d'un composé de la formule (I) ou d'un sel du même pharmaceutiquement acceptable, avec un support pharmaceutiquement acceptable.

BH

ENGLISH ABSTRACT FOR SU1238732

1 / 1 WPAT - ©The Thomson Corp.

Derwent Accession :
1983-56711K [24]

CPI Accession :
C1983-055068

Title :
Alpha-2 antagonist compsn. contg. 3-benzazepine cpd. esp. for reducing intra=ocular pressure and blood pressure

Derwent Class :
B02

Patent Assignee :
(SMIK) SMITHKLINE BECKMAN CORP

Inventor :
DEMARINIS RM; HIEBLE JP; MATTHEWS WD

Nbr of Patents :
19

Nbr of Countries :
27

Patent Number :

EP--80779 A 19830608 DW1983-24 Eng 29p *
AP: 1982EP-0201507 19821129

JP58092616 A 19830602 DW1983-28 Jpn
AP: 1982JP-0201817 19821116

AU8290172 A 19820602 DW1983-29 Eng
AP: 1982AU-0090172 19821104

NO8203990 A 19830620 DW1983-31 Nor
AP: 1982NO-0003990 19821126

FI8203715 A 19830729 DW1983-36 Fin
AP: 1982FI-0003715 19821101

DK8204931 A 19830801 DW1983-37 Dan
AP: 1982DK-0004931 19821105

HUT027615 T 19831028 DW1983-49 Hun

PT--75838 A 19831207 DW1984-02 Por
AP: 1982PT-0075838 19821112

ZA8207887 A 19831018 DW1984-05 Eng
AP: 1982ZA-0007887 19821028

DD-205896 A 19840111 DW1984-19 Ger
AP: 1982DD-0245313 19821129

US4465677 A 19840814 DW1984-35 Eng
AP: 1982US-0398015 19820714

CS8208075 A 19840717 DW1984-40 Cze

ES8405769 A 19841001 DW1984-49 Spa
AP: 1982ES-0517697 19821126

RO--85262 A 19841030 DW1985-18 Rum
AP: 1982RO-0109135 19821125

EP--80779 B 19860716 DW1986-29 Eng
AP: 1982EP-0201507 19821129

DE3272044 G 19860821 DW1986-35 Ger

CA1214165 A 19861118 DW1986-51 Eng
AP: 1982CA-0414027 19821022

SU1238732 A 19860615 DW1987-05 Rus
AP: 1982SU-3513948 19821125

IL--67092 A 19870916 DW1987-47 Eng
AP: 1982IL-0067092 19821027

Priority Number :
1982EP-0305361 19821008; 1981US-0325249 19811127; 1982US-0398015 19820714

Intl Patent Class :
C07D-223/16; A61K-031/33; A61K-031/55; A61P-025/02; A61P-027/02; A61P-027/06; A61P-009/12; C07D-233/00; C07D-233/16; C07D-223/00; A61K-000/00; A61P-025/00; A61P-027/00; A61P-009/00; C07C-000/00; C07D-000/00

Advanced IPC (V8) :
C07D-223/16 [2006-01 A F I R - -]; A61K-031/33 [2006-01 A - I R - -]; A61K-031/55 [2006-01 A L I R - -]; A61K-031/55 [2006-01 A - I R - -]; A61P-025/02 [2006-01 A L I R - -]; A61P-027/02 [2006-01 A L I R - -]; A61P-027/06 [2006-01 A L I R - -]; A61P-009/12 [2006-01 A L I R - -]; C07D-223/16 [2006-01 A - I R - -]; C07D-233/00 [2006-01 A - I R - -]; C07D-233/16 [2006-01 A - I R - -]

Core IPC (V8) :
C07D-223/00 [2006 C F I R - -]; A61K-000/00 [2006 S - I R - -]; A61K-031/33 [2006 C - I R - -]; A61K-031/55 [2006 C L I R - -]; A61K-031/55 [2006 C - I R - -]; A61P-025/00 [2006 C L I R - -]; A61P-027/00 [2006 C L I R - -]; A61P-009/00 [2006 C L I R - -]; C07C-000/00 [2006 S - I R - -]; C07D-000/00 [2006 S - I R - -]; C07D-223/00 [2006 C - I R - -]; C07D-233/00 [2006 C - I R - -]

US Patent Class :
514213000 540594000

Designated States :
EP--80779
Regional States: AT BE CH DE FR GB IT LI LU NL SE
EP--80779
Regional States: AT BE CH DE FR GB IT LI LU NL SE

Abstract :
EP--80779 A
An alpha-2 antagonist compsn. comprises a carrier and a 3-benzazepine cpd. of formula (I) or its pharmaceutically acceptable acid addn. salt. (R is 1-3C alkyl or allyl. X is halo). Most pref. (I) is 6-chloro -2,3,4,5-tetrahydro-3-methyl-1H-benzazepine (Ia) used as its hydrochloride salt. Esp. (I) are used to reduce intraocular pressure (treatment of glaucoma); as cardiovascular agents (treatment of congestive heart failure, angina pectoris and thrombosis) and as antihypertensives. They have no direct effect on pupil size and no effect on heart rate or blood pressure in normotensive subjects.

Manual Codes :
CPI: B06-D04 B12-E01 B12-F01 B12-F02 B12-F05 B12-H02 B12-L04

Update Basic :
1983-24

Update Equiv. :
1983-28; 1983-29; 1983-31; 1983-36; 1983-37; 1983-49; 1984-02; 1984-05; 1984-19; 1984-35; 1984-40; 1984-49; 1985-18; 1986-29; 1986-35; 1986-51; 1987-05; 1987-47